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Case Report

Low-dose cyclosporin therapy for recombinant erythropoietin-induced pure red-cell aplasia

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Introduction

Pure red-cell aplasia (PRCA) is an uncommon condition. It has been reported to occur in dialysis patients following recombinant erythropoietin therapy, initiated for treatment of anaemia of chronic renal failure [1–3]. In those patients, anti-erythropoietin antibodies have been recorded. Little is known of the natural history of this disease or the safest, most efficacious therapy. Here we describe a patient with only moderate renal impairment, who also developed epoetin-induced PRCA. Initial bone marrow histology failed to make a clear diagnosis. There was no spontaneous remission, but the patient was managed successfully with low-dose cyclosporin alone without compromising renal function.

Case

A 46-year-old woman with a 28 year history of type I diabetes mellitus, diabetic nephropathy and hypertension attended the nephrology services with slowly declining chronic renal impairment. Her previous medical history was remarkable for diabetic microvascular disease (retinopathy, peripheral neuropathy), left below-knee amputation (1997) for Charcot joint, and uncomplicated deep venous thrombosis (1991).

She suffered anaemia, controlled at between 95 and 105 g/l on oral iron for 4 years. Her haemoglobin (Hb) fell to 78 g/l, with a normochromic, normocytic blood film. Her glomerular filtration rate (GFR) was 37 ml/min. Iron stores were depleted [ferritin 26, transferrin saturation (Tsat) 28%]. Following a course of i.v. iron (1 g), her Hb was 82 g/l. Subcutaneous epoetin-α was commenced (6000 U/week). During 8 weeks, her Hb rose to 111 g/l. Epoetin-α was reduced to 3000 U/week and further i.v. iron was given (ferritin 56, Tsat 23%). Hb was stable at 100 g/l.

Four weeks later, her Hb fell to 87 g/l. Epoetin-α was increased to 6000 U/week. The patient presented with lethargy and exertional dyspnoea. Hb was 61 g/l, reticulocytes 3×10^9/l (25–85) and platelets 116×10^9/l (150–350). Epoetin-α was increased to 9000 U/week; 3 U of red-cell concentrate (RCC) were given and bone marrow aspiration with trephine was performed. The trephine was generally hypocellular, with relative reduction in mature erythroid islands. No abnormal cells were seen; iron stores were adequate. The histological conclusion was of anaemia of chronic disease.

This diagnosis did not tally with the clinical picture. Epoetin-α was curtailed. Further investigations were carried out: vitamin B_{12} and folate were normal, haemolysis screen negative, Ham's test negative, C-reactive protein and autoantibody screen normal, immunoglobulins and electrophoresis normal, parvovirus B19 titres over 3 months showed no evidence of infection; hepatitis virology, cytomegalovirus (CMV) and Epstein–Bar virus (EBV) titres repeatedly showed no evidence of disease. A CT scan of the thorax, abdomen and pelvis was normal. Anti-microbials, clindamycin and clarithromycin for low-grade amputation stump infection were stopped. Anti-hypertensives, metoprolol and lisinopril were discontinued. No benefit was observed. Despite regular RCC transfusions, Hb fell to 41 g/l; reticulocytes were 1×10^9/l (Figure 1). Platelets remained depressed at $89–138 \times 10^9$/l. In addition to increased frequency of RCC transfusion, epoetin-α was recommenced at 6000 U/week. A repeat marrow aspirate with trephine was performed, but was inadequate. A third aspirate was successful: erythroid precursors were rarely seen, with a markedly increased myeloid to erythroid ratio. Haemoglobinization was normal. No dysplastic cells were seen. Marrow cytogentic studies were negative. Other lineages were normally represented, confirming the histological

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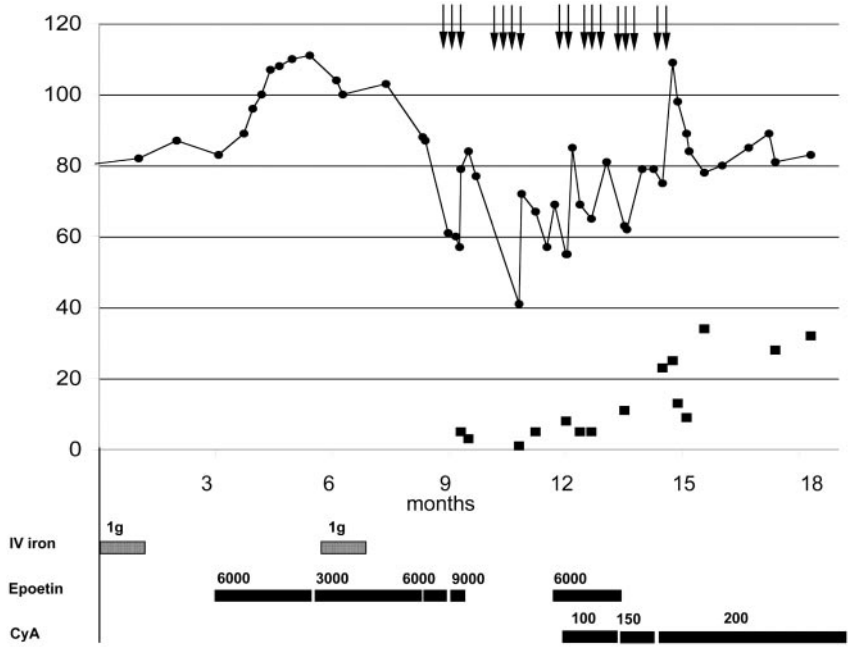

Fig. 1. Chart showing haemoglobin (circles, g/l) and reticulocyte count (squares, $\times 10^9$/l) against time. Therapies with i.v. iron (dose/treatment period), epoetin (U/week) CyA (mg/day) and RCC transfusions (↓per unit) are demonstrated.

diagnosis of PRCA. A working diagnosis of idiopathic PRCA was made.

In view of diabetes mellitus, it was decided to avoid corticosteroids [4,5]. Cyclosporin A (CyA) [6] was introduced, with careful monitoring of blood pressure (BP) and renal function. Initially a low dose of 50 mg b.d. (1.6 mg/kg/day) was commenced. Once its tolerability was determined, the dose was increased to 75 mg b.d., then 100 mg b.d. (3.3 mg/kg/day) to achieve a target 12 h trough level of $\leq$100 nmol/l. GFR and BP remained stable. After therapy had been commenced, serum was analysed using a bioassay for anti-erythropoietin antibodies. The bioassay utilized a red-cell precursor cell line. A 1 ml aliquot of the patient's serum neutralized 19.5 U of epoetin; control serum did not neutralize epoetin. The patient's serum was strongly positive. Thus the patient did not have idiopathic PRCA but erythropoietin-induced PRCA. In light of this result, epoetin-α, which had been re-introduced as part of the therapy for management of idiopathic PRCA, was withdrawn. Five weeks later, reticulocytes were 25×10^9/l. Twelve weeks after commencing CyA, and 7 weeks after increasing the dose to 100 mg b.d., the patient was independent of RCC transfusion. Reticulocytes stabilized at $>30 \times 10^9$/l with Hb between 80 and 90 g/l. Platelets returned to the normal range. The bioassay for anti-erythropoietin antibodies was repeated 16 weeks after commencing CyA. A 1 ml aliquot of the patient's serum now neutralized only 5.0 U of epoetin. Whilst the result remained positive, it was dramatically reduced. Thirty-two weeks after commencing CyA, no neutralizing antibodies were detectable in the serum.

Discussion

PRCA, though rare, is well recognized. Many cases are idiopathic. A proportion of these subsequently manifest myelodysplasia or leukaemias. Many idiopathic cases have antibodies circulating that inhibit growth of erythroid progenitors cultured *in vitro*. In others, erythroid suppression appears to be T cell dependent. Only rarely have antibodies to endogenous erythropoietin been described in idiopathic PRCA [7,8], and only on one occasion have they been demonstrated to be functional [7].

Our case of PRCA had anti-erythropoietin antibodies in the serum. Combined with onset 4 months after the successful introduction of epoetin-α, it was likely that the development of autoantibodies was a direct consequence of administration of recombinant protein. This association was first suggested in 1993 [9], and again in case reports in 1996, and 1997 [2,3]. In none, however, was the association as clearly characterized. Recently, 13 patients with epoetin-induced PRCA have been reported [1]. Twelve had end-stage renal failure and received regular haemodialysis. They had a variety of renal lesions, though none had diabetic glomerulonephropathy. The latency between introduction of epoetin and onset of PRCA varied from 3 to 67 months. None had a precipitating event and none showed spontaneous recovery after withdrawal of epoetin. Thus our case shares some features with those in the case series [1]. In none of the epoetin-induced PRCA cases reported to date, however, has there been an association with thrombocytopenia, as was found here. This association has been recognized

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previously in idiopathic PRCA [10]. Our case emphasizes that it is not exclusively dialysis patients who are at risk, but anyone taking epoetin. Further, it serves to heighten awareness of PRCA in patients receiving epoetin who experience an unexplained fall in Hb. Importantly, if epoetin-induced PRCA is diagnosed, epoetin should be withdrawn, which, in other circumstances of falling Hb, would be counter-intuitive.

Successful management of idiopathic PRCA has been reported using prednisolone with cyclophosphamide or CyA [6,11,12]. As a second line agent, CyA alone has been reported to induce remission in up to 65% of idiopathic cases [13]. In those case series of idiopathic PRCA, the dose of CyA was 12 mg/kg/day, a dose which might be precluded in patients with chronic renal failure and hypertension. There are no reports of CyA monotherapy as a treatment for epoetin-induced PRCA.

Although the mechanism of epoetin-induced PRCA appears to be antibody mediated whereas in idiopathic PRCA only rarely is this the case, our patient was treated with CyA. She rapidly went into remission with relatively low doses of CyA (1.6–3.3 g/kg/day), without the need for concomitant prednisolone. Despite having a reduced GFR, renal function has been stable for 4 months whilst on treatment (creatinine 200–240 μmol/l prior to epoetin-α, currently 237). BP has remained well controlled without additional anti-hypertensives. To date, the only other therapeutic strategies reported to induce remission in epoetin-induced PRCA are corticosteroids alone, steroids combined with cyclophosphamide, or steroids with plasmapheresis and i.v. immunoglobulin [1].

In the series of idiopathic PRCA managed with immunosuppression, therapy was slowly tapered 3 months after achieving remission [13]. The relapse rate has been reported at 80%, 24 months after inducing remission [10]. In the series of epoetin-induced PRCA [1], no information was presented about immunosuppressive withdrawal but, following withdrawal of epoetin, the titre of anti-erythropoietin antibodies slowly declined. This was hastened by immunosuppressives. Unfortunately, the decline in titre did not necessarily correlate with clinical remission. If one can extrapolate from the management of other immunologically mediated diseases, it would appear logical to attempt slow withdrawal of immunosuppressive therapy once antibodies are no longer detectable.

Conclusion

This case emphasizes the need to consider the diagnosis of epoetin-induced PRCA in any patient developing transfusion-dependent anaemia following the introduction of epoetin. In the absence of spontaneous remission following withdrawal of epoetin, trial of low-dose CyA should be considered.

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Conflict of interest statement. None declared.

References

1. Casadevall N, Nataf J, Viron B *et al*. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; 346: 469–475
2. Peces R, de la Torre M, Alcazar R, Urra JM. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; 335: 523–524
3. Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997; 47: 331–335
4. Jannot-Lamotte MF, Raccah D. Management of diabetes during corticosteroid therapy. *Presse Med* 2000; 29: 263–266
5. Kim YS, Kim MS, Kim SI *et al*. Post-transplantation diabetes is better controlled after conversion from prednisone to deflazacort: a prospective trial in renal transplants. *Transpl Int* 1997; 10: 197–201
6. Means RT, Jr, Dessypris EN, Krantz SB. Treatment of refractory pure red cell aplasia with cyclosporine A: disappearance of IgG inhibitor associated with clinical response. *Br J Haematol* 1991; 78: 114–119
7. Casadevall N, Dupuy E, Molho-Sabatier P, Tobelem G, Varet B, Mayeux P. Autoantibodies against erythropoietin in a patient with pure red-cell aplasia. *N Engl J Med* 1996; 334: 630–633
8. Peschle C, Marmont AM, Marone G, Genovese A, Sasso GF, Condorelli M. Pure red cell aplasia: studies on an IgG serum inhibitor neutralizing erythropoietin. *Br J Haematol* 1975; 30: 411–417
9. Garcia JE, Senent C, Pascual C *et al*. Anaphylactic reaction to recombinant human erythropoietin. *Nephron* 1993; 65: 636–637
10. Dessypris EN. The biology of pure red cell aplasia. *Semin Hematol* 1991; 28: 275–284.
11. Lacy MQ, Kurtin PJ, Tefferi A. Pure red cell aplasia: association with large granular lymphocyte leukemia and the prognostic value of cytogenetic abnormalities. *Blood* 1996; 87: 3000–3006
12. Marmont A, Peschle C, Sanguineti M, Condorelli M. Pure red cell aplasia (PRCA): response of three patients to cyclophosphamide and/or antilymphocyte globulin (ALG) and demonstration of two types of serum IgG inhibitors to erythropoiesis. *Blood* 1975; 45: 247–261
13. Marmont AM. Therapy of pure red cell aplasia. *Semin Hematol* 1991; 28: 285–297

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